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Meta-analysis of the effect of the halothane gene on 6 variables of pig meat quality and on carcass leanness[1]

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ABSTRACT: Technological meat quality is a significant economic factor in pork production, and numerous publications have shown that it is strongly influenced both by genetic status and by rearing and slaughter conditions. The quality of meat is often described by meat pH at different times postmortem, as well as by color and drip loss, whereas carcass quality is often characterized by lean percentage. A meta-analysis of findings relating to 3,530 pigs reported in 23 publications was carried out to assess the effects of the halothane gene, sex, breed, and slaughter weight of animals on 7 selected variables: pH at 45 min postmortem, ultimate pH, reflectance (L*-value), redness (a*-value), yellowness (b*-value), drip loss, and lean percentage. Two statistical methods were used in the meta-analysis: the method of effect size and the better known random effects model. The method of effect size was associated with Markov chain Monte Carlo techniques for implementing Bayesian hierarchical models to avoid the problems of limited data and publication bias. The results of our meta-analysis showed that the halothane genotype had a significant effect on all analyzed pork quality variables. Between-study variance was evaluated with the Cochran (1954) *Q*-test of heterogeneity. Meta-regression was used to explain this variance, with covariates such as breed, sex, slaughter weight, and fasting duration being integrated into different regression models. The halothane gene effect was associated with the breed effect only for the following variables: L*-value, b*-value, and drip loss. Slaughter weight contributed significantly only to the explanation of differences in ultimate pH between homozygous genotypes. In response to inconsistencies reported in the literature regarding the difference between the genotypes NN and Nn, results of the meta-analysis showed that the difference between these 2 genotypes was significant for all the analyzed variables except the a*-value.

Key words: halothane gene, meat quality, meta-analysis, pig

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INTRODUCTION

Pork quality depends on genetic factors, environmental factors, and their interactions. A number of publications (Sellier and Monin, 1994) suggest that pork quality is strongly influenced by the effect of overall genetic type, by individual genes (especially the halothane and RN genes), and by rearing and slaughter conditions. Although the mutated halothane "n" allele is considered fully recessive, there is conflicting information regarding the meat quality of heterozygous animals (Monin et al., 1999; Channon et al., 2000; Miller et al., 2000). Another unresolved debate concerns the effect of the halothane gene on ultimate pH in LM (Larzul et al., 1997; Fisher et al., 2000). In response to these gaps in the scientific literature, we chose to combine existing results in a meta-analysis (i.e., an analysis combining published results in a statistically sound way; DuMouchel, 1990). This method is particularly useful when results from independent studies are contradictory because it increases statistical power (Cucherat et al., 2002).

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The aim of this study was to use meta-analysis to estimate the effect of the halothane gene on 6 of the most important pig meat quality attributes: muscle pH measured 45 min (**pH45**) or 24 h (ultimate pH; **pHu**) postmortem, color coordinates (L*, a*, and b*), and drip loss (**DL**). For carcass quality, we analyzed the difference in lean percentage (**lean%**) between NN and Nn animals. Statistically, we compared 2 meta-analytical methods: the conventional random effects (**RE**) regression method and the effect size method. The RE regression method is commonly used in animal production studies, whereas the effect size method refers to the classical meta-analysis approach commonly performed in medical studies. The latter is considered more suitable for meta-analysis of a small number of studies but has the disadvantage that it allows only pairwise comparison between the analyzed factor levels.

MATERIALS AND METHODS

Animal Care and Use Committee approval was not obtained for this study because the data were obtained from an existing database.

Data Collection

For meat quality, the criterion for selecting publications was that they reported the effect of the halothane gene on 1 or more measurements of pork quality and compared the 3 halothane genotypes (NN, Nn, and nn). The measurements of pork quality extracted from studies were all taken in LM; they included pH45, pHu, objective color measurements determined with a Minolta Chroma Meter (CIE L* as a score of reflectance, a* as a score of redness, and b* as a score of yellowness; CIE, 1978) measured 24 h postmortem, and DL as a measurement of weight loss determined after 24 or 48 h of storage at 4°C and expressed as a percentage of the initial weight of a muscle sample. For carcass quality, the criterion for selecting publications was that they reported the effect of the halothane gene on lean%. Only the comparison of NN and Nn was retained. The studies had to be published as reviewed papers or conference proceedings, in English or in French, after 1990 for the halothane status to be established through molecular genotyping (Fujii et al., 1991). The search was conducted through the Web of Science bibliographic database (http://www.isiwebofknowledge.com/).

The database included general information (e.g., titles, author names, dates of publication), experimental qualities (e.g., preslaughter treatment, feed composition, breed, sex, and castrate status), and other quantitative data (e.g., slaughter weight, slaughter age, statistics used in the original analysis that were necessary for the present meta-analysis). Only 6 publications were excluded because they compared only the 2 genotypes NN and Nn for all the analyzed attributes except lean%. Publications reporting several experiments were dealt with by assigning a specific code for each experiment. Each observation in the meta-analysis corresponded to the mean of each treatment group. The selected publications were further required to provide intraexperiment variation, expressed either as SEM (or SE) or SD, for the mean of each treatment group. Publications in which this information was missing were excluded. The bibliographic search yielded a total of 55 studies. Selection for an effect of the halothane gene on the 7 analyzed attributes narrowed this number to 23 publications published between 1990 and 2008 and 74 experimental groups (see Appendix Table A1), representing 3,530 pigs. In the sensitivity analysis, the influence of each individual study was evaluated by estimating overall effect size in the absence of one or more studies. Five studies were excluded in the context of sensitivity analysis.

Statistical Analysis

Effect Size Method. The effects of the halothane gene on pH45, pHu, L*, a*, and b* were evaluated using the mean difference or effect size method described by Whitehead and Whitehead (1991). For DL and lean%, the standardized effect size was used because the measurement methods for these 2 attributes differed from 1 study to another (Whitehead, 2002). The effect size method allows the comparison of 2 population groups (i.e., a treatment and a control group). The effect size (θ) was calculated as the difference between the means of 2 genotypes for each attribute. For example, in the comparison NN vs. nn, NN was considered the control group and nn was considered the treatment group. The standardized effect size was estimated by dividing this difference by its pooled SD. Reported SE, and the number of animals in the treatment and control groups, were used to calculate the pooled SD of each effect size (Searle et al., 1992). Effect size estimates on data pooled across experiments were obtained with a fixed effects model (Mantel and Haenszel, 1959). The general fixed effects model is given by $\widehat{\theta}_i = \theta + \varepsilon_i$, for $(i = 1,\ldots,r)$, where r is the number of studies, $\hat{\theta}$ is the maximum likelihood estimate of the effect size in study i, θ is the common effect size, and ε_i is the error term for the ith study. Effects were assumed to be normally distributed: $\widehat{\theta}_i \sim N\left(\theta, \sigma_\varepsilon^2\right)$.

Forest plots, showing the point estimate and the 95% confidence interval (**CI**) of the individual experiment-level effect size, were used to visualize the data. The plots of the 3 halothane genotype comparisons for each attribute are included as online-only data supplements (http://jas.fass.org/content/vol88/issue9/).

The global null hypothesis that the treatment difference in all studies was equal to zero was tested using the association test U (Whitehead, 2002). This test was performed by comparing the statistic

$$U = \frac{\left(\sum_{i=1}^{r} \widehat{\theta}_i w_i\right)^2}{\sum_{i=1}^{r} w_i}$$

with the χ^2 with 1 df, where w_i is the inverse of the variance of the effect size θ_i.

Variation in experiment-level effect size was assessed with a χ^2 test of heterogeneity, denoted as the Q^2-test. The null hypothesis was that the treatment effect would be the same across all r trials. The null hypothesis was rejected if the heterogeneity test statistic was greater than a critical value that separated the upper 5% of a χ^2 with $(r-1)$ df (Cochran, 1954). With heterogeneous data, an RE model was used to estimate effect size by considering study a random factor (Der Simonian and Laird, 1986). The general RE model is given by $\widehat{\theta}_i = \theta + \nu_i + \varepsilon_i$, where ν_i is the RE of study i, $\nu_i \sim N(0, \tau^2)$, and τ^2 is the between-study variance. It follows that $\widehat{\theta}_i \sim N\left(\theta, \sigma_\varepsilon^2 + \tau^2\right)$.

The heterogeneity of results among trials was quantified using the I^2-statistic (Higgins and Thompson, 2002). The I^2-statistic described the proportion of the total study variance that was due to between-study variation; it was calculated as

$$I^2 = \frac{Q^2 - (r-1)}{Q^2} \times 100.$$

Where I^2-values were greater than 50%, a meta-regression was carried out to explore the source of the heterogeneity. Meta-regression formally tests whether there is evidence for different effects in different subgroups of trials. Meta-regression extended the RE meta-analysis by including one or more covariates to explain heterogeneity in treatment effects.

A Bayesian hierarchical model was adopted when data were heterogeneous, especially in the meta-regression of effect size, to estimate the model parameters. The analysis was performed using Markov chain Monte Carlo methods through the Bayesian computation software Winbugs (Spiegelhalter et al., 2003). In total, 10,000 iterations were dismissed as burn-in and the following 500,000 iterations were used for parameter estimations. Satisfactory convergence of the simulated Markov chains to the target posterior distribution was assessed using the diagnostics in Winbugs. The Bayesian estimations of the overall and covariate effects were made systematically where the heterogeneity test was significant. Both regression and Bayesian methods were applied in effect size estimations; it was therefore convenient to define the phrase "significantly different from 0" to cover both the situation in which there was a 95% CI that did not include 0, and a Bayesian 95% CI that did not include 0.

Publication bias was investigated using funnel plots (Light and Pillemer, 1984). In these funnel plots, a measure of study size is shown on the horizontal axis and effect size is plotted on the vertical axis. It was expected that, in the absence of bias, the plot would resemble a symmetrical funnel on its side. If there was bias, for example, because smaller studies showing no statistically significant effects remained unpublished, the plot would be asymmetrical. In these situations, the effect calculated in the meta-analysis might have been overestimated. Unfortunately, the small number of experiments eligible for meta-analysis in this study made interpretation of funnel plots difficult. Publication bias was therefore also investigated statistically using the Egger test (Egger et al., 1997), which is more appropriate for a small sample size.

RE Regression Method. This meta-analytical approach involved the application of a regression model to all data. The meta-analytic model included pig genotype, breed, sex (discrete variables), and slaughter weight (continuous variable). Experiment was taken into account as an RE (St-Pierre, 2001).

The linear mixed model was $Y_{ijk} = \mu + S_i + a_j + bX_{ij} + e_{ijk}$, where Y_{ijk} is the independent variable; μ is the overall mean; S_i is the RE of the ith study, assumed as $\sim_{iid} N\left(0, \sigma_s^2\right)$, a_j is the fixed effect of the jth level of factor; b is the overall regression coefficient of Y on X (a fixed effect); X_{ij} is the value of the continuous predictor variable; and e_{ijk} is the residual error, assumed as $\sim_{iid} N\left(0, \sigma_e^2\right)$. The variables e_{ijk} and S_i are assumed to be independent random variables. In view of the limited number of data, interactions between different factors were not included. Covariates that were not significant at a P-value of 0.05 were removed from the model.

To account for unequal variance among studies, all variables were weighed by the reciprocal inverse of their squared SE. In addition, an unstructured variance-covariance matrix was assumed for the random part of the model. The covariance parameter was considered different from 0 if the P-value was less than 0.10. A P-value greater than the traditional $P = 0.05$ was used because accurate estimations of variances and covariances require a considerable number of observations (St-Pierre, 2001). Computation was carried out using the MIXED procedure (SAS Inst. Inc., Cary, NC). All models were evaluated for the assumptions of normality and constant variance. The test for normality used the UNIVARIATE procedure of SAS. A Levene test of the residuals ($P < 0.05$) was used to test the assumption of constant variance.

To test the robustness of the results, an analysis of interstudy variability was carried out by comparing interstudy variance with intrastudy variance. It was recommended that it be stated, before the analysis, what size of estimated variance attributable to study would be considered negligible (Sauvant et al., 2008). In our study, the proportion of the total study variance that

Table 1. Summary of effect size, Q^2-test,[1] and I^2-statistic[2] for the halothane genotype comparisons

			Heterogeneity			
Outcome[3]	θ_i [4] (95% CI)	*P*-value	Q^2-test	df	*P*-value	I^2
NN vs. nn						
pH45	0.536 (0.377, 0.695)	<0.001	135.59	10	<0.0001	92.62
pHu	0.054 (0.007, 0.100)	<0.05	34.31	10	<0.001	70.84
L*	−3.386 (−3.996, −2.776)	<0.0001	15.29	12	>0.05	21.51
a*	−0.318 (−0.547, −0.089)	<0.05	20.8	12	>0.05	42.55
b*	−0.965 (−1.162, −0.768)	<0.001	20.41	12	>0.05	41.22
DL	−1.668 (−2.711, −0.626)	<0.01	43.05	12	<0.001	72.12
NN vs. Nn						
pH45	0.188 (0.139, 0.238)	<0.001	25.07	10	<0.01	60.10
pHu	0.029 (0.0001, 0.058)	<0.05	19.46	10	>0.05	48.61
L*	−0.732 (−1.259, −0.204)	<0.05	15.16	12	>0.05	20.87
a*	−0.136 (−0.336, 0.063)	>0.05	16.76	12	>0.05	28.39
b*	−0.467 (−0.754, −0.179)	<0.001	35.69	12	<0.001	66.38
DL	−0.389 (−1.279, 0.500)	>0.1	45.35	12	<0.001	73.54
Lean%	−0.975 (−1.248, −0.701)	<0.001	14.21	10	>0.05	29.63
Nn vs. Nn						
pH45	0.333 (0.221, 0.446)	<0.001	90.71	10	<0.001	88.97
pHu	0.015 (−0.003, 0.034)	>0.05	11.85	10	>0.05	15.68
L*	−2.497 (−3.092, −1.902)	<0.0001	20.4	12	>0.05	43.94
a*	−0.088 (−0.318, 0.140)	>0.05	18.19	12	>0.05	34.03
b*	−0.405 (−0.765, −0.045)	<0.001	45.49	12	<0.001	72.41
DL	−1.303 (−2.162, −0,444)	<0.01	33.01	12	<0.001	63.70

[1]Chi-square test of heterogeneity.
[2]Proportion of the total study variance attributable to the between-study variation.
[3]ph45 = pH at 45 min postmortem; pHu = ultimate pH; L* = reflectance; a* = redness; b* = yellowness; DL = drip loss.
[4]Pooled effect size was estimated using a fixed effects model when the Q^2-test was not significant; conversely, the estimation was made using a random effects model when the Q^2-test was significant.

was attributable to interstudy variation was computed as

$$\rho = \frac{\sigma_s^2}{\sigma_s^2 + \sigma_e^2},$$

following the method described by Hox and de Leeuw (2003), where σ_s^2 represents the variation between studies and σ_e^2 is the sampling variance. The variances σ_s^2 and σ_e^2 were estimated using a REML method. As in the effect size method, when the ρ-statistic exceeded 50%, a meta-regression was carried out to explain the between-study variability.

RESULTS

Effect of the Halothane Gene on pH45 and pHu

A significant effect of the halothane gene on pH45 was confirmed by both methods (Tables 1, 2, and 3), with differences between the 3 genotypes being significant. Meta-regression may better explain the effect size heterogeneity for the comparison Nn vs. nn because the difference between these 2 genotypes was partly explained by fasting duration ($P = 0.008$) when it varied between 10 and 24 h. However, the Bayesian estimation of the effect of fasting time failed to confirm the results of the meta-regression; that is, the CI of the fasting time effect estimation included 0, implying that fasting time could not be considered significant (Table 4). Unexpectedly, the regression method showed that the effect of the halothane gene on pH45 was significantly influenced by sex ($P = 0.0002$), which explained almost 78% of the variability between the combined studies (Table 2).

Based on the effect sizes derived from studies examining the effect of the halothane gene on pHu (Table 1), differences between NN and nn ($\theta = 0.054$; $P < 0.05$) and between NN and Nn ($\theta = 0.029$; $P < 0.05$) were significant. However, pHu differences between Nn and nn were not significant ($\theta = 0.015$; $P > 0.05$).

A fixed effects model was used to compare the effect size estimations of the comparisons NN vs. Nn and Nn vs. nn because the corresponding heterogeneity tests were not significant (Table 1). Posterior means, SD, and 95% CI for the overall and covariate effects for pHu and pH45 are listed in Table 4. The existing heterogeneity between effect size for the comparison between NN vs. nn was partially explained by the significant effect of slaughter weight, which explained 25% of the between-study variance of effect size between the NN and nn genotypes. Slaughter weight in the range of 85 to 125 kg had a significant negative effect on pHu differences between homozygous genotypes.

Table 2. Least squares means ± SE of the analyzed meat quality traits according to halothane genotype estimated using the random effects regression model, and *P*-values of the tested covariates for meta-regression

	Halothane genotype				*P*-value		
Outcome[1]	NN	Nn	nn	*P*-value	Breed	Sex	Slaughter wt
pH45	6.40 ± 0.06	6.24 ± 0.06	5.92 ± 0.07	0.0001	0.060	0.0002	0.520
pHu	5.63 ± 0.05	5.59 ± 0.05	5.57 ± 0.05	0.0036	0.538	0.529	0.583
L*	50.08 ± 0.72	50.69 ± 0.70	53.39 ± 0.71	0.00008	0.0002	0.300	0.990
a*	7.50 ± 0.26	7.67 ± 0.25	7.93 ± 0.26	0.1672	0.0001	0.080	0.209
b*	10.99 ± 0.4	11.42 ± 0.4	12.11 ± 0.4	0.0001	0.0001	0.310	0.510
DL	3.77 ± 0.34	4.12 ± 0.36	5.16 ± 0.42	0.0146	0.172	0.807	0.382
Lean%	57.8 ± 1.12	58.78 ± 1.12	—[2]	0.0004	0.07	0.059	0.040

[1]ph45 = pH at 45 min postmortem; pHu = ultimate pH; L* = reflectance; a* = redness; b* = yellowness; DL = drip loss; lean% = lean percentage.
[2]Comparison was not made.

Table 3. Difference (least squares mean ± SE) of the analyzed meat quality traits according to halothane genotype estimated using the random effects regression model

Outcome[1] and genotypes compared	Difference	*P*-value	R^2, %	I^2, %
pH45			86.48	49.1
NN vs. nn	0.481 ± 0.0642	<0.0001		
NN vs. Nn	0.162 ± 0.048	<0.01		
Nn vs. nn	0.319 ± 0.063	<0.0001		
pHu			93.12	95.4
NN vs. nn	0.061 ± 0.016	0.0011		
NN vs. Nn	0.043 ± 0.015	<0.05		
Nn vs. nn	0.017 ± 0.015	>0.1		
L*			96.91	84.34
NN vs. nn	−3.315 ± 0.473	<0.0001		
NN vs. Nn	−0.607 ± 0.469	>0.1		
Nn vs. nn	−2.707 ± 0.468	<0.0001		
a*			97.71	78.58
NN vs. nn	−0.432 ± 0.220	>0.05		
NN vs. Nn	−0.170 ± 0.219	>0.1		
Nn vs. nn	−0.262 ± 0.221	>0.1		
b*			99.73	95.93
NN vs. nn	−1.120 ± 0.170	<0.0001		
NN vs. Nn	−0.430 ± 0.150	<0.01		
Nn vs. nn	−0.680 ± 0.170	<0.001		
DL			49.36	41.32
NN vs. nn	−1.388 ± 0.439	0.0042		
NN vs. Nn	−0.345 ± 0.373	>0.1		
nNn vs. nn	−1.043 ± 0.447	<0.05		
Lean%			97.92	98.53
NN vs. Nn	−0.981 ± 0.180	<0.001		

[1]ph45 = pH at 45 min postmortem; pHu = ultimate pH; L* = reflectance; a* = redness; b* = yellowness; DL = drip loss; lean% = lean percentage.

Table 4. Summary of posterior distribution of pooled effect size and effects of significant covariates for pHu and pH45 obtained from Bayesian meta-regression

Outcome[1] and genotypes compared	Intercept (95% CI[2])	Covariate[3] coefficient (95% CI)	Between-study variance	Intrastudy variance	I^2, %
pH45					
NN vs. nn	0.536 (0.358, 0.717)		0.0817	0.0041	95.15
NN vs. Nn	0.189 (0.133, 0.247)		0.0054	0.0020	73.02
Nn vs. nn	0.341 (0.216, 0.472)	−0.064 (−0.186, 0.067)	0.0341	0.0044	88.49
pHu					
NN vs. nn	0.061 (0.016, 0.104)	−0.054 (−0.101, −0.006)	0.0033	0.0012	72.37

[1]ph45 = pH at 45 min postmortem; pHu = ultimate pH.
[2]CI = confidence interval.
[3]The significant covariate for pHu was the slaughter weight ($P = 0.04$), and the significant covariate for pH45 was the fasting time ($P = 0.008$).

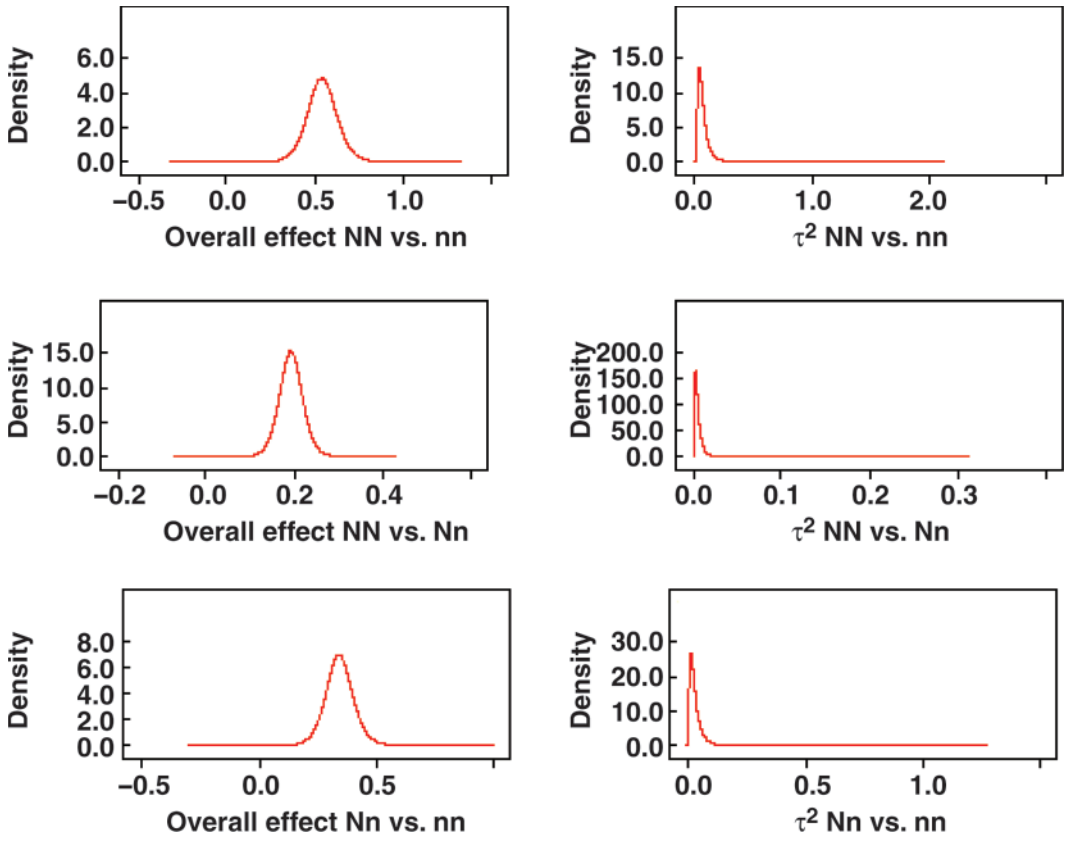

Figure 1. Posterior predictive distributions from the meta-analysis model for the overall effect and τ^2 (between-study variance) of pH at 45-min postmortem comparisons between the 3 halothane genotypes.

As demonstrated in Figures 1 and 2, the overall effect of fit of the model was satisfactory. For the pHu comparison NN vs. nn and the 3 halothane genotype comparisons for pH45, the posterior predictive distributions of the test statistics (overall effect and between-study variance) included the observed value of the statistic in areas of reasonable probability.

The results of the RE regression method showed a significant effect of the halothane gene on pHu (Table 2). The comparison of least squares mean differences between the 3 halothane genotypes showed that, as in the effect size method, differences between NN and nn and between NN and Nn were significant ($P = 0.0011$ and $P = 0.011$, respectively), whereas the difference between Nn and nn was not significant ($P = 0.24$; Table 3). None of the tested covariates was able to explain the increased heterogeneity between studies (Table 2).

Effect of the Halothane Gene on Color Coordinates: L, a*, and b**

The heterogeneity tests of effect size estimations for the attributes L* and a* were not significant; therefore, the fixed effects model was retained (Table 1). The analysis of L* effect sizes showed that halothane genotype had a significant effect on the 3 halothane genotype comparisons: NN vs. Nn, NN vs. Nn, and Nn vs. nn. However, the analysis of a* effect sizes showed that only differences between the NN and nn genotypes were significant (Table 1). With regard to the b* attribute, comparisons between the 3 halothane genotypes were all significantly different from 0 (Table 1). The estimated effect sizes of the comparisons NN vs. Nn and Nn vs. nn were heterogeneous. The effect of halothane genotype on differences between Nn and nn

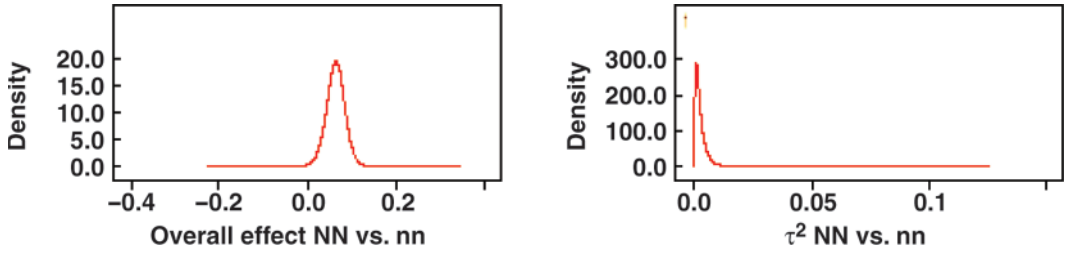

Figure 2. Posterior predictive distributions from the meta-analysis model for the overall effect and τ^2 (between-study variance) of ultimate pH comparison between the NN and nn genotypes.

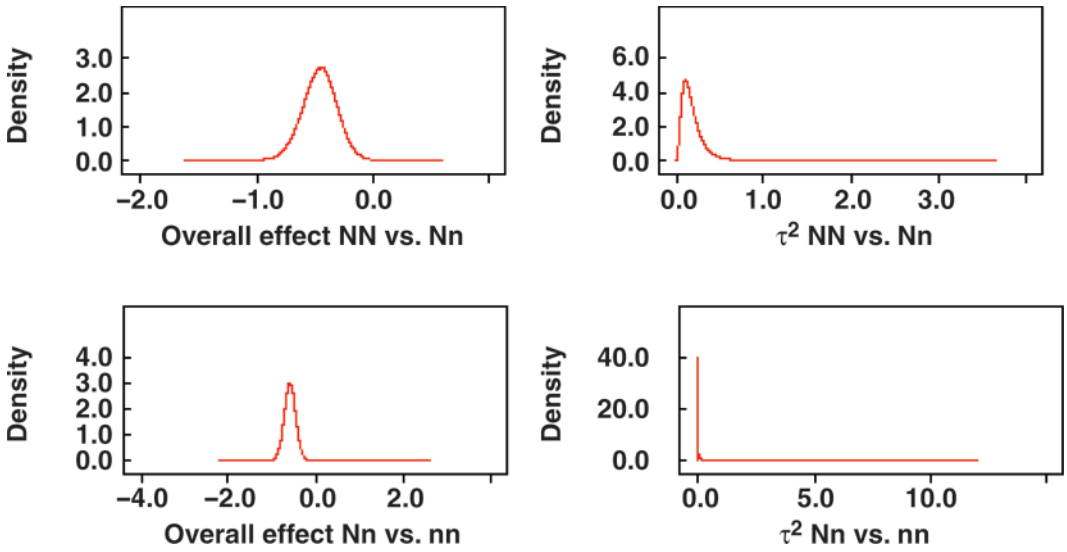

Figure 3. Posterior predictive distributions from the meta-analysis model for the overall effect and τ^2 (between-study variance) of yellowness comparisons between the genotypes NN vs. Nn and Nn vs. nn.

was associated with a significant effect of breed, which explained approximately 80% of the between-study variance (Table 2). Heterogeneity between the NN and Nn genotypes was not influenced by any of the tested covariates. Posterior means and CI of the overall effect and different breed level effects are listed in Table 5. Predictive distributions of the posterior overall effect and between-study variance for the b* comparisons NN vs. Nn and Nn vs. nn are illustrated in Figure 3.

According to the results of the regression method, the halothane gene had a significant effect on L* and b*; however, its effect on a* was not significant. The increased heterogeneity between studies was explained mainly by breed ($P = 0.0002$, $P < 0.0001$, and $P < 0.0001$, respectively, for L*, a*, and b*; Table 2).

Effect of the Halothane Gene on DL

Significant differences in DL attributable to the halothane gene effect were found for NN vs. nn and for Nn vs. nn (Table 1 and Figure 4). Because the heterogeneity test was significant for the 3 halothane genotype comparisons, meta-regression was used to explain the between-study variance, in particular for the comparisons NN vs. nn and Nn vs. nn, where the overall effect was significant ($\theta = -1.67$, $P = 0.008$, and $\theta = -1.303$, $P < 0.01$, respectively). Breed explained 79 and 73% of the between-study variability for NN vs. nn and Nn vs. nn comparisons, respectively.

The Bayesian estimation of the overall effect for the comparison NN vs. Nn did not confirm the effect size method results (Table 5 and Figure 2). The CI did not cover 0, and the null hypothesis of a zero overall effect was therefore rejected.

Drip loss data included in the model of the RE regression method were not standardized because they are weighed by the inverse of their reciprocal variance in the SAS statement. As in the RE model estimation of the effect size method, the RE regression results showed that only the differences NN vs. nn and Nn vs. nn were significant (Table 3). The proportion of between-study variance in total variability was not large in the RE regression method ($\rho < 50\%$), but the determination coefficient R^2 was very small. This apparent

Table 5. Summary of posterior distribution of pooled effect size obtained from Bayesian meta-regression by considering of breed as a covariate for b* and DL

Outcome[1] and genotypes compared	Intercept (95% CI[2])	Between-study variance	Intrastudy variance	I^2, %
b*				
NN vs. Nn	−0.461 (−0.778, −0.165)	0.184	0.093	0.664
Nn vs. nn	−0.622 (−0.894, −0.349)	0.057	0.131	0.303
DL				
NN vs. nn	−0.608 (−0.887, −0.331)	0.078	0.109	0.417
NN vs. Nn	−0.184 (−0.653, −0.264)	0.529	0.102	0.838
Nn vs. nn	−0.485 (−0.744, −0.226)	0.060	0.112	0.349

[1]b* = yellowness; DL = drip loss.
[2]CI = confidence interval.

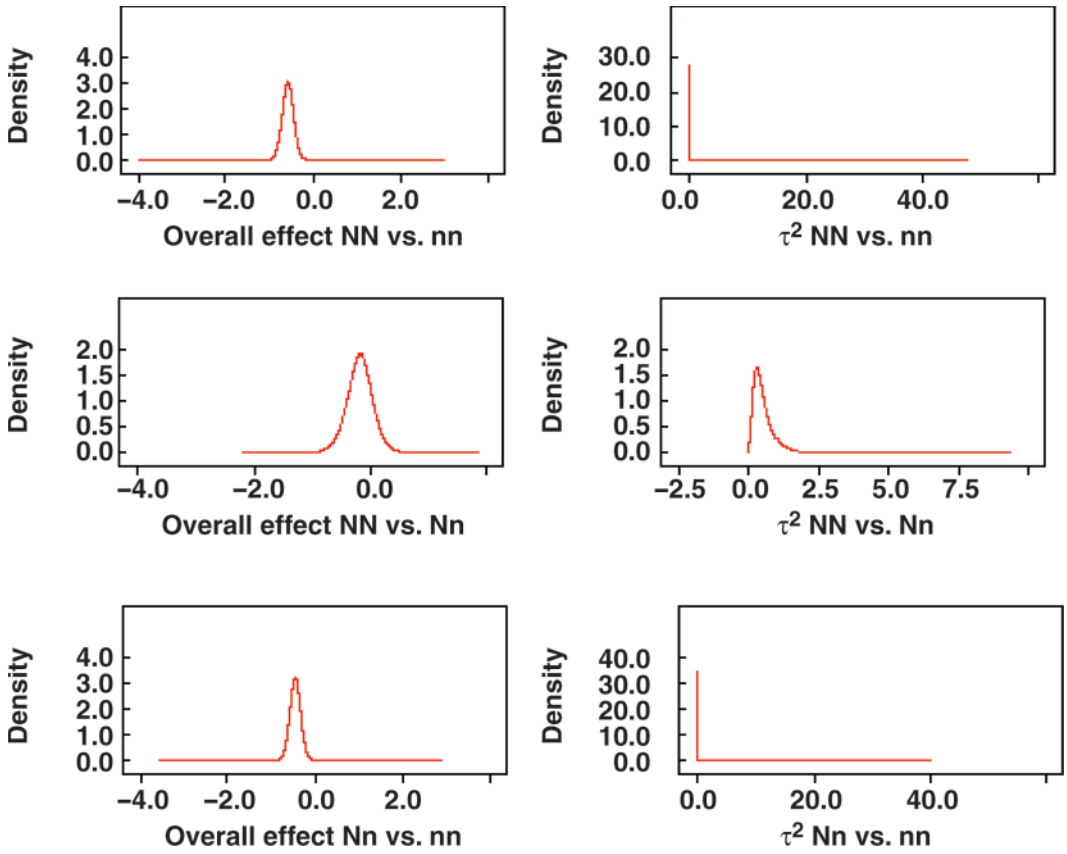

Figure 4. Posterior predictive distributions from the meta-analysis model for the overall effect and τ^2 (between-study variance) of drip loss comparisons between the 3 halothane genotypes.

contradiction could be explained by the difference in the scale of measurement in each study.

Effect of the Halothane Gene on Lean%

Only a few studies provided data related to lean% of nn pigs. Therefore, the analysis of this attribute was made only between NN and Nn pigs. In this analysis, the results obtained from both meta-analysis methods were consistent (Tables 1 and 3). As with DL, the effect size of lean% was estimated as a standardized mean difference. The heterogeneity test of effect size of the combined studies was not significant. The estimation of the overall effect following a fixed effect model showed that the halothane gene had a highly significant effect on differences between the NN and Nn genotypes ($P < 0.001$).

The combined data in the RE regression method were not standardized. Consequently, heterogeneity between studies was very high ($\rho = 99\%$). None of the tested covariates was significant (Table 2). Comparison between the effect size estimation of lean% between the NN and Nn genotypes and the least squares mean difference between these 2 genotypes revealed similar values for both methods. Indeed, the effect size estimation was −0.975 (−1.248, −0.701) and the RE estimation of the least squares mean difference was −0.983 (−1.33, −0.628). Additionally, both of these values are well within the CI of each other.

DISCUSSION

In this study, 2 meta-analytic methods were used to quantify the effect of the halothane gene on a range of key attributes of pork quality in pig populations. The synthesis of published data in the form of a meta-analysis is increasingly common in the area of animal production. It has been shown to be a useful tool for obtaining precise predictions of the response of a given phenomenon to quantitative or qualitative variations (Sauvant et al., 2008).

Our selection of analyzed attributes was made after an extensive bibliographic research, which indicated that pH45, pHu, color variables (L*, a*, and b*), and DL are the main components or predictive traits for technological and sensory pork quality, and that carcass lean% is an important predictive trait for carcass quality (Sellier, 1998). The data set used in the present study was prepared after a comprehensive search of the internationally published literature. Qualitative comparison of the literature indicated that the effect of the halothane gene on the main attributes of technological pig meat quality is controversial, especially where the 7 attributes listed above are concerned. In-

deed, our meta-analysis for each attribute, except for pH45 and lean%, included the results of studies with diametrically opposed conclusions (i.e., that the halothane gene had a significant and a nonsignificant effect on the analyzed traits).

Because the effect of preslaughter conditions, and of their interactions with genotype and breed, on pork quality is already known (Mormède et al., 1984; Terlouw et al., 1997; Hay and Mormède, 1998; Désautés et al., 1999), we limited our selection to studies with a similar experimental design. This helped us avoid any kind of bias in the combined results and, consequently, in the meta-analysis results. Nevertheless, characteristics that differed between studies and that could explain interstudy heterogeneity included breed, sex, slaughter weight, and fasting duration.

The synthesis of the results of the meta-analysis confirmed that the halothane gene had a significant effect on all the analyzed attributes except the color attribute a*. The results of the Egger test (Egger et al., 1997) for publication bias showed a significant bias for the comparison NN vs. Nn for color coordinates and for the comparison Nn vs. nn for pH45. Given this publication bias, the results from our meta-analysis might slightly overestimate these effects.

The effect of the halothane gene on pHu has been the subject of debate. Several studies have shown this gene to have no significant effect on pHu changes in LM (Guéblez et al., 1995; Larzul et al., 1996). Other research has shown significant differences for pHu attributable to the halothane genotype (Klont et al., 1994; Fisher et al., 2000). According to the results of our meta-analysis, the 2-by-2 comparison of pHu differences between genotypes showed that only the difference between Nn and nn was not significant, and that the NN genotype had a greater pHu than the Nn and nn genotypes. Interestingly, results of the effect size method showed that the difference between NN and nn was affected by slaughter weight. The difference between the 2 genotypes tended to decrease with slaughter weight. This can be contrasted with the results of Sather et al. (1991a,b), who found that the effect of the halothane allele in the heterozygous state depended on slaughter weight, but also that the effect of the halothane allele appeared to be recessive in lightweight pigs and became dominant in heavyweight pigs. The apparent contradiction between our results and those of Sather et al. (1991a,b) may be due to breed differences between the sets of studies. However, this halothane genotype × slaughter weight interaction was not confirmed by Garcia-Macias et al. (1996), Leach et al., (1996), and Larzul et al. (1997).

Another unresolved issue in the literature concerned the value of heterozygous animals. In keeping with a systematic review based on 13 studies conducted by Sellier (1998), our results showed that the Nn animals were positioned between NN and nn animals for most meat quality traits, although the corresponding values were closer to those of NN than to those corresponding to nn for the attributes pH45, L*, and DL. Despite their proximity, differences between NN and Nn animals were significant for all the analyzed attributes except a*.

In this paper we have compared 2 meta-analytical approaches: the conventional RE regression method based on a frequentist approach (St-Pierre, 2001; Sauvant et al., 2008) and the effect size method completed with a Bayesian approach when data were heterogeneous (Cusack et al., 1996; Wood et al., 2006). Both methods are well established in animal production research, although the first is predominantly used in cases where the numbers of data are large, whereas the effect size method tends to be used when data are limited. The effect size method therefore appeared to be better suited for our meta-analysis (with a small number of combined studies and discrete variables). However, this method allows only pairwise comparison between the analyzed factors. Our use of Bayesian methods was facilitated by Markov chain Monte Carlo algorithms, which allowed for more flexibility in the formulation of prior information and models and for a wider range of inferences and comparisons through simulation. Whatever the method, the differences estimated between genotypes for L*, a*, and lean%, and also for some comparisons of pHu (comparisons NN vs. Nn and Nn vs. nn) and b* (comparison NN vs. nn), were very close. This consistency is explained by the data homogeneity for these comparisons proved by the Cochran (1954) test of heterogeneity. In the RE regression method, heterogeneity that was due to between-study variance remained greater even after considering breed as a covariate in the models. It should be noted that the slight differences existing between the effect size estimations and the least squares mean differences between genotypes for the above-mentioned attributes were most likely because, in the effect size method, the estimation assumed a fixed effects model, whereas, in the RE regression method, estimations assumed a mixed model.

With pHu, the effect size method enabled us to reduce heterogeneity between studies. This reduction in heterogeneity was mainly due to the possibility, allowed by this method, of showing the significant effect of slaughter weight on pHu differences between the homozygous genotypes. By contrast, the RE regression method did not reveal any significant effect of the tested covariates, even though the heterogeneity between studies was very high.

With DL and lean%, the possibility of standardizing data when measurement methods were different was an advantage of the effect size method. The standardized effect size method allowed us to reduce the variability considerably between studies for DL, except for the comparison NN vs. Nn. Variability between studies for the DL comparisons NN vs. nn and Nn vs. nn was mainly explained by the significant effect of breed, which is known to be one of the most important factors influencing technological and sensory pig meat quality (Bout and Girard, 1988; Sellier and Monin, 1994).

Discrepancies between methods were found for DL. The overall effect of the halothane gene on the DL difference between NN and Nn was not significant when considering the results from the effect size method as well as the RE regression method. Bayesian estimation of the overall effect between these 2 genotypes was significant, however. To explain this inconsistency, we should mention that in a classical, non-Bayesian approach to the effect size method using a fixed or RE model, the effect size θ and the variances σ_{ε}^2 and τ^2 are considered fixed variables and the between-study variance τ^2 is mostly estimated via an approximation proposed by DerSimonian and Laird (1986). In a general hierarchical Bayesian scheme (DuMouchel, 1990), σ_{ε}^2 and τ^2 are assumed to be random variables. The distributions of these quantities are specified a priori. It is standard practice to assume a "flat" or "uninformative" prior for θ, as was done in the present study, because even with a small number of studies, the combined data become relatively informative regarding the location of the prior distribution of the effect size (Carlin, 1992). The imposition of distributions on θ, σ_{ε}^2, and τ^2 allows a more explicit description of any underlying variability in the way the study outcomes are distributed. This in turn allows considerable flexibility in application. Moreover, it can be viewed as a Bayesian generalization of the RE model of effect size. The present study showed that there was a considerable indication of heterogeneity between studies and that moving to a Bayesian approach could provide more accurate estimates of effect size.

Meta-analysis was a useful tool with which to address existing controversies about the halothane gene effect generated by existing studies in a statistically robust way. Our study confirmed the significant effect of the halothane gene on all the analyzed attributes except a*. It also confirmed the intermediate position of Nn animals between NN and nn animals for most quality traits. By and large, the 2 methods investigated here yielded similar conclusions. However, discrepancies appeared when heterogeneity between studies was increased, which was the case with DL between the NN and Nn genotypes. In this case, the Bayesian approach, implemented in the effect size method, emerged as the most appropriate form of meta-analysis.

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APPENDIX

Table A1. Summary of the 23 references used to construct the final database

Code[1]	Reference	Halothane genotype	Pig breed[2]	Sex	Slaughter wt, kg	pHu[3]	pH45[3]	L*[3]	a*[3]	b*[3]	DL[3]	Lean%[3]
Study 1	De Smet and al. (1996)	NN	BL	Castrated and gilts	100	5.59 ± 0.013	6.25 ± 0.030	50.8 ± 0.40	7.60 ± 0.15	13.80 ± 0.11	3.80 ± 0.27	59.10 ± 0.38
		Nn	P × BL	Castrated and gilts	100	5.60s ± 0.010	6.09 ± 0.021	51.0 ± 0.29	7.40 ± 0.11	13.70 ± 0.08	4.60 ± 0.19	59.60 ± 0.31
		nn	P × BL	Castrated and gilts	100	5.57 ± 0.024	5.76 ± 0.050	54.7 ± 0.69	7.40 ± 0.26	15.00 ± 0.20	6.00 ± 0.46	61.40 ± 0.59
Study 2	Fisher et al. (2000)	NN	L × LW	Castrated and gilts	86	5.62 ± 0.032	6.22 ± 0.051	42.0 ± 0.47	5.51 ± 0.18	6.74 ± 0.20	—	67.50 ± 0.39
		Nn	L × LW	Castrated and gilts	86	5.60 ± 0.038	5.94 ± 0.061	43.5 ± 0.56	5.40 ± 0.22	6.67 ± 0.24	—	68.10 ± 0.47
		nn	L × LW	Castrated and gilts	86	5.44 ± 0.041	5.36 ± 0.066	45.6 ± 0.61	5.81 ± 0.24	7.20 ± 0.26	—	69.70 ± 0.51
Study 3	Fernandez et al. (2002), Exp. 1	NN	P × LW	Castrated	105	5.52 ± 0.03	6.52 ± 0.05	53.6 ± 1.10	5.90 ± 0.40	4.10 ± 0.20	—	—
		Nn	P × LW	Castrated	105	5.48 ± 0.01	6.19 ± 0.09	54.7 ± 0.70	6.30 ± 0.40	3.90 ± 0.20	—	—
		nn	P × LW	Castrated	105	5.46 ± 0.03	5.65 ± 0.09	60.9 ± 1.60	7.50 ± 0.60	5.70 ± 0.50	—	—
Study 4	Fernandez et al. (2002), Exp. 2	NN	P × LW	Castrated	105	—[4]	—	48.2 ± 1.10	5.70 ± 0.50	3.00 ± 0.20	—	—
		Nn	P × LW	Castrated	105	—	—	51.3 ± 1.10	7.10 ± 0.60	3.90 ± 0.20	—	—
		nn	P × LW	Castrated	105	—	—	52.6 ± 1.10	7.10 ± 1.10	4.10 ± 0.50	—	—
Study 5	Larzul et al. (1996)	NN	P × LW	Castrated and gilts	112	5.52 ± 0.02	6.36 ± 0.03	—	—	—	—	—
		Nn	P × LW	Castrated and gilts	112	5.55 ± 0.02	6.13 ± 0.03	—	—	—	—	—
		nn	P × LW	Castrated and gilts	112	5.60 ± 0.03	5.65 ± 0.04	—	—	—	—	—
Study 6	Hanset et al. (1995)	NN	P × LW	Castrated and gilts	105	6.01 ± 0.01	6.15 ± 0.02	—	—	—	—	63.17 ± 0.13
		Nn	P × LW	Castrated and gilts	105	5.96 ± 0.01	5.91 ± 0.01	—	—	—	—	63.95 ± 0.10
		nn	P × LW	Castrated and gilts	105	5.95 ± 0.01	5.80 ± 0.02	—	—	—	—	65.54 ± 0.14
Study 7	McPhee and Trout (1995), Exp. 1	NN	LW × L	Gilts	96	5.84 ± 0.07	6.40 ± 0.05	50.8 ± 0.40	7.60 ± 0.15	13.80 ± 0.11	3.80 ± 0.27	—
		Nn	LW × L	Gilts	96	5.89 ± 0.08	6.23 ± 0.05	51.0 ± 0.29	7.40 ± 0.11	13.70 ± 0.08	4.60 ± 0.19	—
		nn	LW × L	Gilts	96	5.90 ± 0.09	5.96 ± 0.06	54.7 ± 0.69	7.40 ± 0.26	15.00 ± 0.20	6.00 ± 0.46	—
Study 8	McPhee and Trout (1995), Exp. 2	NN	LW × L	Gilts	96	5.54 ± 0.05	6.41 ± 0.09	—	—	—	5.98 ± 0.57	—

Continued

Table A1 (Continued). Summary of the 23 references used to construct the final database

Code[1]	Reference	Halothane genotype	Pig breed[2]	Sex	Slaughter wt, kg	pHu[3]	pH45[3]	L*[3]	a*[3]	b*[3]	DL[3]	Lean%[3]
		Nn	LW × L	Gilts	96	5.51 ± 0.05	6.18 ± 0.08	—	—	—	6.29 ± 0.56	—
		nn	LW × L	Gilts	96	5.50 ± 0.06	5.52 ± 0.11	—	—	—	4.89 ± 0.72	—
Study 9	Klont and Lambooy (1995a)	NN	L	Castrated	82	5.59 ± 0.05	6.65 ± 0.04	55.83 ± 1.40	5.50 ± 0.35	14.64 ± 0.15	3.80 ± 0.49	—
		Nn	L × BL	Castrated	82	5.46 ± 0.05	6.38 ± 0.05	58.67 ± 0.92	5.66 ± 0.45	15.45 ± 0.37	3.70 ± 0.42	—
		nn	BL	Castrated	82	5.44 ± 0.04	6.08 ± 0.14	57.95 ± 1.18	6.10 ± 0.26	15.10 ± 0.35	8.10 ± 1.25	—
Study 10	Klont et al. (1994)	NN	L	Castrated	100	5.67 ± 0.03	6.74 ± 0.04	52.53 ± 0.98	5.45 ± 0.25	13.90 ± 0.28	2.60 ± 0.30	—
		Nn	L × BL	Castrated	100	5.56 ± 0.03	6.66 ± 0.02	55.91 ± 0.97	6.39 ± 0.22	15.33 ± 0.25	3.10 ± 0.30	—
		nn	BL	Castrated	100	5.53 ± 0.02	6.55 ± 0.05	56.97 ± 0.58	6.05 ± 0.22	15.18 ± 0.16	4.40 ± 0.50	—
Study 11	Klont et al. (1993)	NN	L	Castrated	120	5.58 ± 0.03	6.73 ± 0.04	49.83 ± 1.32	7.58 ± 0.35	14.06 ± 0.49	—	—
		Nn	L × BL	Castrated	120	5.57 ± 0.05	6.68 ± 0.05	52.63 ± 1.37	7.11 ± 0.49	14.59 ± 0.47	—	—
		nn	BL	Castrated	120	5.56 ± 0.04	6.63 ± 0.07	53.80 ± 1.34	6.64 ± 0.43	14.59 ± 0.27	—	—
Study 12	Kocwin-Podsiadla et al. (1995)	NN	PL	Castrated and gilts	100	5.51 ± 0.03	6.23 ± 0.05	—	—	—	—	—
		Nn	PL	Castrated and gilts	100	5.47 ± 0.03	6.11 ± 0.07	—	—	—	—	—
		nn	PL	Castrated and gilts	100	5.48 ± 0.03	5.71 ± 0.10	—	—	—	—	—
Study 13	Depreux et al. (2002)	NN	C1	Gilts	120	—	—	42.37 ± 0.6	10.51 ± 0.36	10.15 ± 0.25	5.68 ± 0.43	—
		Nn	C1	Gilts	120	—	—	42.56 ± 0.6	10.77 ± 0.36	10.65 ± 0.25	3.91 ± 0.43	—
		nn	C1	Gilts	120	—	—	46.24 ± 0.7	10.71 ± 0.43	11.08 ± 0.28	5.55 ± 0.51	—
Study 14	Klont and Lambooy (1995b), Exp. 1	NN	L	Castrated	115	—	—	54.80 ± 1.13	6.75 ± 0.59	14.76 ± 0.36	2.80 ± 0.40	—
		Nn	L × BL	Castrated	115	—	—	54.59 ± 0.87	7.45 ± 0.42	15.11 ± 0.29	4.20 ± 0.60	—
		nn	BL	Castrated	115	—	—	57.48 ± 1.12	6.05 ± 0.51	14.82 ± 0.31	5.90 ± 1.10	—
Study 15	Klont and Lambooy (1995b), Exp. 2	NN	L	Castrated	115	—	—	56.56 ± 1.48	5.85 ± 0.38	14.55 ± 0.30	3.60 ± 0.30	—
		Nn	L × BL	Castrated	115	—	—	58.22 ± 2.23	6.74 ± 0.64	15.16 ± 0.33	6.60 ± 1.10	—

Continued

Table A1 (Continued). Summary of the 23 references used to construct the final database

Code[1]	Reference	Halothane genotype	Pig breed[2]	Sex	Slaughter wt, kg	pHu[3]	pH45[3]	L*[3]	a*[3]	b*[3]	DL[3]	Lean%[3]
		nn	BL	Castrated	115	—	—	58.07 ± 1.56	6.28 ± 0.56	14.89 ± 0.35	8.40 ± 1.10	—
Study 16	Tam et al. (1998), Exp. 1	NN	C2	Castrated and gilts	80	—	—	49.10 ± 0.64	10.96 ± 0.26	13.48 ± 0.21	3.24 ± 0.37	—
		Nn	C2	Castrated and gilts	80	—	—	48.68 ± 0.64	11.18 ± 0.26	14.21 ± 0.21	2.30 ± 0.37	—
		nn	C2	Castrated and gilts	80	—	—	50.11 ± 0.71	11.84 ± 0.29	15.14 ± 0.24	4.18 ± 0.41	—
Study 17	Tam et al. (1998), Exp. 2	NN	C2	Castrated and gilts	115	—	—	49.44 ± 0.67	12.81 ± 0.36	14.70 ± 0.26	5.83 ± 0.44	—
		Nn	C2	Castrated and gilts	115	—	—	49.63 ± 0.67	13.03 ± 0.36	15.51 ± 0.25	3.92 ± 0.44	—
		nn	C2	Castrated and gilts	115	—	—	52.68 ± 0.75	12.60 ± 0.41	15.70 ± 0.29	5.94 ± 0.52	—
Study 18	Lahucky et al. (1997)	NN	C3	Castrated and gilts	90	—	—	—	—	—	4.00 ± 0.90	—
		Nn	C3	Castrated and gilts	90	—	—	—	—	—	7.90 ± 0.70	—
		nn	C3	Castrated and gilts	90	—	—	—	—	—	8.60 ± 0.90	—
Study 19	Aalhus et al. (1997)	NN	Lac	Castrated and gilts	106	—	—	—	—	—	3.77 ± 0.32	—
		Nn	Lac	Castrated and gilts	106	—	—	—	—	—	4.33 ± 0.32	—
		nn	Lac	Castrated and gilts	106	—	—	—	—	—	4.70 ± 0.32	—
Study 20	Franco et al. (2008)	NN	P × LW × L	Castrated and gilts	90	—	—	—	—	—	2.08 ± 0.29	55.56 ± 0.54
		Nn	P × LW × L	Castrated and gilts	90	—	—	—	—	—	2.76 ± 0.37	56.31 ± 0.67
		nn	P × LW × L	Castrated and gilts	90	—	—	—	—	—	3.40 ± 0.42	58.04 ± 0.77
Study 21	Leach et al. (1996)	NN	Pic405 × PicCamborough[5]	Castrated and gilts	125	—	—	—	—	—	—	53.80 ± 0.70
		Nn	Pic405 × PicCamborough	Castrated and gilts	125	—	—	—	—	—	—	55.10 ± 0.70
Study 22	Fàbrega et al. (2002)	NN	P × (L × LW)	Gilts	115	—	—	—	—	—	—	58.69 ± 0.27
		Nn	(LW × P) × (L × LW)	Gilts	115	—	—	—	—	—	—	60.85 ± 0.49
Study 23	Sather et al. (1998)	NN	L × (LW × L)	Castrated and gilts	110	—	—	—	—	—	—	55.50 ± 0.37
		Nn	L × (LW × L)	Castrated and gilts	110	—	—	—	—	—	—	56.80 ± 0.38
Study 24	Eggert et al. (2002)	NN	LW × L	Gilts	125	—	—	—	—	—	—	50.22 ± 1.32

Continued

Table A1 (Continued). Summary of the 23 references used to construct the final database

Code[1]	Reference	Halothane genotype	Pig breed[2]	Sex	Slaughter wt, kg	pHu[3]	pH45[3]	L*[3]	a*[3]	b*[3]	DL[3]	Lean%[3]
		Nn	LW × L	Gilts	125	—	—	—	—	—	—	50.42 ± 1.32
Study 25	Kortz et al. (2004)	NN	(P × D) × (PLW × PL)	Castrated and gilts	100	—	—	—	—	—	—	53.21 ± 0.46
		Nn	(P × D) × (PLW × PL)	Castrated and gilts	100	—	—	—	—	—	—	53.45 ± 0.36
Study 26	Apple et al. (2002)	NN	(D × H) × (Y × L)	Castrated and gilts	110	—	—	—	—	—	—	46.60 ± 2.60
		Nn	(D × H) × (Y × L)	Castrated and gilts	110	—	—	—	—	—	—	52.10 ± 2.60
Study 27	Bridi et al. (2003)	NN	Cambrough22 × AGPIC419[6]	Castrated	90	—	—	—	—	—	—	54.40 ± 0.30
		Nn	Cambrough22 × AGPIC419	Castrated	90	—	—	—	—	—	—	56.00 ± 0.29

[1]Code identification of each experiment included in the meta-analysis. This code was used in the forest plots to describe each data set.

[2]List of breeds and crosses used in each experiment. Abbreviations: BL = Belgian Landrace; P = Piétrain; L = Landrace; LW = Large White; PL = Polish Landrace; C1 = composite 1 (an American commercial breed); C2 = composite 2 (an American commercial breed); C3 = composite 3 (crosses of 4 breeds: Yorkshire, Landrace, Piétrain, and Duroc); Lac = Laconie; D = Duroc; PLW = Polish Large White; H = Hampshire; Y = Yorkshire.

[3]Mean ± SE. pHu = ultimate pH; ph45 = pH at 45 min postmortem; L* = reflectance; a* = redness; b* = yellowness; DL = drip loss; lean% = lean percentage.

[4]Data not given by the reference.

[5]Commercial crossbred from lines of Pig Improvement Company Inc. (Franklin, KY).

[6]Crossbred of Cambrough22 (commercial crossbred from lines of Pig Improvement Company, Grong Grong, New South Wales, Australia) and AGPIC419 (commercial crossbred from lines of Agroceres Company, Rio Claro-São Paulo, Brazil).